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Cost-Effectiveness Models for Chronic Obstructive Pulmonary Disease: Cross-Model Comparison of Hypothetical Treatment Scenarios

Martine Hoogendoorn, PhD[1,*], *Talitha L. Feenstra, PhD*[2,3], *Yumi Asukai, MSc*[4], *Sixten Borg, MSc*[5,6], *Ryan N. Hansen, PharmD, PhD*[7], *Sven-Arne Jansson, PhD*[8], *Yevgeniy Samyshkin, MSc*[4], *Margarethe Wacker, MSc*[9], *Andrew H. Briggs, DPhil*[10], *Adam Lloyd, MPhil*[4], *Sean D. Sullivan, PhD*[7], *Maureen P.M.H. Rutten-van Mölken, PhD*[1]

[1]*Institute for Medical Technology Assessment, Erasmus University, Rotterdam, The Netherlands;* [2]*Department for Prevention and Health Services Research, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands;* [3]*Department of Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands;* [4]*IMS Health, Health Economics and Outcomes Research, Real-World Evidence Solutions, London, UK;* [5]*The Swedish Institute for Health Economics, Lund, Sweden;* [6]*Health Economics Unit, Department of Clinical Sciences Malmö, Lund University, Lund, Sweden;* [7]*Pharmaceutical Outcomes Research and Policy Program, School of Pharmacy, University of Washington, Seattle, WA, USA;* [8]*The OLIN Studies, Luleå, Sweden;* [9]*Helmholtz Zentrum München, Institute of Health Economics and Health Care Management, Member of the German Center for Lung Research, Comprehensive Pneumology Center Munich, Neuherberg, Germany;* [10]*Institute of Health & Wellbeing, University of Glasgow, Glasgow, UK*

ABSTRACT

Objectives: To compare different chronic obstructive pulmonary disease (COPD) cost-effectiveness models with respect to structure and input parameters and to cross-validate the models by running the same hypothetical treatment scenarios. **Methods:** COPD modeling groups simulated four hypothetical interventions with their model and compared the results with a reference scenario of no intervention. The four interventions modeled assumed 1) 20% reduction in decline in lung function, 2) 25% reduction in exacerbation frequency, 3) 10% reduction in all-cause mortality, and 4) all these effects combined. The interventions were simulated for a 5-year and lifetime horizon with standardization, if possible, for sex, age, COPD severity, smoking status, exacerbation frequencies, mortality due to other causes, utilities, costs, and discount rates. Furthermore, uncertainty around the outcomes of intervention four was compared. **Results:** Seven out of nine contacted COPD modeling groups agreed to participate. The 5-year incremental cost-effectiveness ratios (ICERs) for the most comprehensive intervention, intervention four, was €17,000/quality-adjusted life-year (QALY) for two models, €25,000 to €28,000/QALY for three models, and €47,000/QALY for the remaining two models. Differences in the ICERs could mainly be explained by differences in input values for disease progression, exacerbation-related mortality, and all-cause mortality, with high input values resulting in low ICERs and vice versa. Lifetime results were mainly affected by the input values for mortality. The probability of intervention four to be cost-effective at a willingness-to-pay value of €50,000/QALY was 90% to 100% for five models and about 70% and 50% for the other two models, respectively. **Conclusions:** Mortality was the most important factor determining the differences in cost-effectiveness outcomes between models.

Keywords: COPD, cost-effectiveness, model, validation.

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic condition characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lungs to noxious particles or gases [1]. Most important respiratory symptoms are cough, sputum production, and dyspnea. Patients regularly experience exacerbations, which are periods of increased symptoms, often leading to increased use of health care, hospital admission, or even death [2–6]. Prevalence estimates of COPD are as high as 11.4% to 26.1% for the population older than 40 years [7]. COPD is associated with a significant impairment of quality of life and substantial health care use, especially in the more severe stages [8]. The Global Burden of Disease study 2010 showed that COPD is the third leading cause of death and the ninth cause of disability-adjusted life-years worldwide [9,10]. In most Western countries, age-specific prevalence rates are stable or decreasing in men but increasing in women. Because of aging of the population, the absolute number of patients is still expected to increase substantially in the coming decade. COPD is projected to be the fifth leading cause of disability worldwide in 2030 [11]. This puts

* *Address correspondence to:* Martine Hoogendoorn, Institute for Medical Technology Assessment, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands.
E-mail: hoogendoorn@bmg.eur.nl.

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increasing pressure on health care expenditures, which are already rising by 4% each year in European countries [12]. It also puts pressure on the limited capacity of pulmonary hospital wards. Against this background, information on the cost-effectiveness of the increasing number of treatment options for COPD becomes more and more important to guide reimbursement decision making. Such information can be obtained from clinical trials. But in a slowly progressing disease such as COPD, these trial data are often complemented with cost-effectiveness models that facilitate extrapolation of trial data to a longer time horizon and comparisons between treatments that have not been compared head-to-head in a clinical trial.

In the last decade, several cost-effectiveness models for COPD were published. Inspired by the Mount Hood Challenge Meetings for diabetes modelers, the authors M.H., T.F., and M.R. took the initiative to organize a round-the-table meeting in 2011 for COPD modeling groups to present their model, discuss data availability, and share their experience. A second meeting focusing on cross-validation was organized in 2012. The different modeling groups were asked to run the same prespecified hypothetical interventions with their model after standardizing (part of) the input parameters. This way the effect of differences in input variables and/or assumptions between the models was investigated. Such cross-validation is one of the five main types of model validation as described by the ISPOR-SMDM Modeling Good Research Practices Task Force [13].

The aim of this article was to compare different COPD models with respect to structure, input parameters, and implementation and to cross-validate the models by running hypothetical treatment scenarios. This contributes to a better understanding of the effect of different modeling choices on the outcomes.

Methods

Early in 2012, a steering committee of six people experienced in COPD modeling was formed (M.R., T.F., A.B., S.B., A.L., and S.S.). The main task of this committee was to prepare the second modeling meeting (i.e., date, location), discuss the content of the treatment scenarios (i.e., standardization of input parameters, type of interventions), and discuss the current article. In May 2012, several COPD modeling groups were contacted to explore their interest in participating in the second COPD modeling meeting and in running the treatment scenarios with their models. Modeling groups were requested to complete two parts. First, the groups were asked to simulate four hypothetical interventions and compare the results with the situation in which no intervention would have been provided. The second part focused on the types of uncertainty included in the model and the uncertainty around the outcomes of the fourth intervention. Data were reported in a structured Microsoft Excel spreadsheet and returned to the organizers of the meeting 2 weeks before the meeting took place. A structured overview of the results of the different models was provided to all participants during the meeting as input for the discussion. After the meeting, modeling groups were contacted once or twice to provide clarifications or to perform additional or re-analyses.

Overview of Participating Models

In total nine comprehensive COPD models were identified on the basis of a search in PubMed and through personal communication with modelers in the field [14–22]. In total, seven modeling groups agreed to participate [14–20]. The model of Spencer et al. [22] did not participate because the company who funded the work was in the middle of developing a new model. Furthermore, the Burden of Obstructive Lung Disease model was not represented [21], because no modelers of this group could be present at the meeting. All the seven participating models were state-transition models and assumed the Markov property but varied in the number of health states and the duration of a cycle. One patient-level model was included [15]. All models used the Global Initiative for Chronic Obstructive Lung Disease lung function classification published in 2003 to define COPD severity stages [23]. All of them modeled the incidence of COPD exacerbations, but in different ways. For all but one model [18], the maximum time horizon was lifetime. A short description of participating models is given below. Details and data sources for two important parameters, disease progression and mortality, are described in Tables 1 and 2, respectively.

Indacaterol COPD model (by price represented by Asukai) [14]

The indacaterol COPD model published in 2011 was developed to estimate the cost-effectiveness of the bronchodilating agent indacaterol versus other long-acting bronchodilators. The model, funded by Novartis, could be characterized as a state-transition cohort model with a cycle length of 3 months and was constructed in Microsoft Excel. The model had 13 health states: 4 COPD severity states, each further extended by 2 health states for a nonsevere and severe exacerbation, and death. The COPD population at the start was based on two large trials for indacaterol and specified by COPD severity. Disease progression in terms of lung function decline was derived from the Understand Potential Long-term Impacts on Function with Tiotropium trial (Table 1). Mortality was subdivided into COPD-related mortality and all-cause mortality. Mortality due to exacerbations was not modeled separately (Table 2). The model was validated by comparing life expectancy with several epidemiology sources for COPD, which showed that mortality probabilities in the model were similar to external data.

Swedish generic model of disease history and economic impact of COPD (represented by Borg) [15]

The Swedish generic model of disease history and economic impact of COPD was published in 2004 and financed by AstraZeneca. The main purpose of the model, implemented in Splus 2000 Professional, was to evaluate the cost-effectiveness of new interventions for COPD. The model has seven health states: one for mild COPD, two states for moderate, two states for severe, one state for very severe COPD, and death. The model has two health states each for moderate and severe COPD because backward transition is allowed up to one milder health state, but not further. Exacerbation status was modeled as separate states within each severity state and subdivided into exacerbation-free, mild, moderate, and severe exacerbations. The two-dimensional Markov chain model simulated individual patients using two different cycle lengths: 1 year for disease progression and mortality and 1 week for exacerbation status. The model was populated with data on patients with COPD detected during screening of the general population in Northern Sweden, the Obstructive Lung Disease in Northern Sweden studies [24]. Transition probabilities between COPD severity states and mortality were obtained from 10-year follow-up data from the Obstructive Lung Disease in Northern Sweden studies and modeled to depend on age, COPD severity, and exacerbations (Tables 1 and 2). The model used primary data validated against published sources with satisfactory results. For the present work, the model was restored from the archive and set up to execute. The optimized version of the computation engine, however, could not be compiled in the current computer environment and therefore only a limited number of patients could be simulated, resulting in poor precision in the estimates.

Table 1 – Overview disease progression.

Model representative	Framework	Subgroup specifications	Transition probability in the first year for a 65-y-old ex-smoking male patient with moderate COPD
Asukai et al. [14]	Annual decline in lung function of 30 ml/y obtained from the UPLIFT trial used to calculate transition probabilities	No subgroup specification in annual decline	Moderate to severe: 4.3% Moderate to very severe: 0.1%
Borg et al. [15]	Transition probabilities based on the 10-y follow-up data of the OLIN studies. 1. Base risk 2. Risk related to exacerbations	Transition rates specified by COPD disease severity and age	Moderate to mild: 5.0% Moderate to severe: 6.0% Moderate to very severe: 0%
Hansen et al. [16]	Transition probabilities adapted from Atsou et al.: mild/moderate COPD based on the BOLD cohort, for severe to very severe adapted from Hoogendoorn et al. (Lung Health Study)	Transition rates specified by age, smoking status, and COPD disease severity	Moderate to severe: 8.3% Moderate to very severe: 0.3%
Hoogendoorn et al. [17]	Annual decline in lung function obtained from a re-analysis of the original 5-y data of the Lung Health Study	Annual decline specified by sex, age, smoking status, and COPD severity	Moderate to severe: 3.2% Moderate to very severe: 0%
Rutten-van Mölken et al. [18]	First year: Annual decline in lung function as observed in six tiotropium trials. Years 2–5: Annual decline in lung function of 52 ml/y obtained from the Lung Health Study applied to the patient population in two trials to calculate the transition probabilities	No subgroup specification in annual decline	Moderate to severe: 32% Moderate to very severe: 6.6%
Samyshkin et al. [19]	Annual decline in lung function of 52 ml/y obtained from the Lung health Study used to calculate time to transition and transition probabilities	No subgroup specification in annual decline	Moderate to severe: 7.0% Moderate to very severe: 0.4%
Wacker et al. [20]	Annual decline in lung function for mild/ moderate COPD based on the Lung Health Study (smokers: 60 ml/y, former smokers: 27 ml/y), for smokers with severe COPD based on the ISOLDE + TORCH trials. Decline was transformed into time to transition and transition probabilities	Annual decline specified by smoking	Moderate to severe: 1.1% Moderate to very severe: 0.01%

BOLD, Burden of Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; ISOLDE, Inhaled Steroids in Obstructive Lung Disease; OLIN, Obstructive Lung Disease in Northern Sweden; TORCH, Towards a Revolution in COPD Health; UPLIFT, Understand Potential Long-term Impacts on Function with Tiotropium.

US dynamic cohort COPD model (represented by Hansen) [16]

The dynamic cohort COPD model developed in the United States to evaluate the cost-effectiveness of a broad range of COPD interventions was not yet published at the time of the modeling meeting but has been presented during the ISPOR Annual International Meeting of 2012. The model implemented in Microsoft Excel had 16 states: 4 COPD severity stages further subdivided into 3 separate states (stable disease, outpatient or inpatient managed exacerbations), 3 end-stage treatments (i.e., lung rehabilitation, lung volume reduction surgery, and lung transplantation), and death. The starting population of the model represents the US COPD population. Disease progression in terms of transition probabilities to the next severity stage was adapted from Atsou et al. [25], which uses the Burden of Obstructive Lung Disease cohort [20], and Hoogendoorn et al. [26] and is specified by age and smoking status (Table 1). Health-related quality of life was mapped from the St. George Respiratory Questionnaire [27]. Mortality was divided into all-cause mortality and mortality associated with outpatient and inpatient managed exacerbations (Table 2). The model was validated by performing various internal checks and comparison to the Lung Health Study.

Dutch dynamic population COPD progression model (represented by Hoogendoorn) [17,26,28]

The latest version of the Dutch dynamic population COPD progression model was published in 2011 and was used to estimate the cost-effectiveness of a wide range of interventions for COPD. The model sponsored by the Lung Foundation Netherlands is representative for the Dutch COPD population. It is a state-transition model with a cycle length of 1 year and has six main health states: no COPD, four COPD severity stages, and death. Each stage is further specified by sex, 1-year age classes, and smoking status. Moderate and severe exacerbations are modeled as events within each severity state. The model is dynamic because it takes into account changes in the general population due to birth, changes in smoking behavior, and mortality. Changes in the COPD population over time are the result of new incidence, changes in smoking behavior,

Table 2 – Overview mortality after standardization for background mortality.

Model representative	Framework	Subgroup specifications	Probability to die in the first year for a 65-y-old ex-smoking male patient with moderate COPD
Asukai et al. [14]	Total mortality: 1. All-cause mortality obtained from death tables (not adjusted for COPD-specific deaths) 2. COPD-related mortality	 1. Specified by sex and age 2. Specified by COPD disease severity	Total mortality: 2.7% 1. 1.5% 2. 1.2%
Borg et al. [15]	Total mortality: 1. Base mortality 2. Mortality related to severe exacerbations	1. Specified by age and disease severity 2. Specified by age and disease severity	Total mortality: 4.6% (with average number of severe exacerbations)
Hansen et al. [16]	Total mortality: 1. All-cause mortality from life tables 2. Exacerbation-related mortality: relative risks applied to all-cause mortality in the general population associated with moderate and severe exacerbations by COPD stage	 1. All-cause mortality by sex and age 2. Exacerbation-related mortality by COPD disease severity and severity of the exacerbation	Total mortality: 3.6% 1. 1.5% without exacerbation 2. 2.4% with a moderate exacerbation 3. 3.15% with a severe exacerbation
Hoogendoorn et al. [17]	Total mortality: 1. Mortality due to other causes including other smoking-related diseases 2. COPD-attributable mortality excluding mortality due to exacerbations 3. Exacerbation-related mortality	 1. Specified by sex, age, and smoking status 2. Specified by sex, age, and COPD disease severity 3. Specified by age	Total mortality: 6.0% 1. 1.5% 2. 2.2% 3. 2.3%
Rutten-van Mölken et al. [18]	Total mortality	Specified by COPD disease severity	Total mortality: 6.6%
Samyshkin et al. [19]	Total mortality: 1. Non–COPD-related mortality 2. Increased COPD-related mortality including a 7.7% case fatality associated with a severe exacerbation	 1. Specified by sex and age 2. Specified by COPD disease severity	Total mortality: 2.9% 1. 1.5% 2. 1.4%
Wacker et al. [20]	Total mortality: 1. Mortality in stable disease – Background mortality – COPD-related mortality 2. Mortality associated with severe exacerbations (surgery and transplantation <60 y)	 1. Specified by age, COPD disease severity, and smoking 2. Specified by age (and disease stage, smoking status for AE mortality)	Total mortality: 7.4% 1. 3.5% – 1.5% – 2.0% 2. 3.9%

AE, adverse event; COPD, chronic obstructive pulmonary disease.

disease progression, and mortality. Disease progression was modeled as annual decline in lung function specified by sex, age, smoking status, and disease severity on the basis of a re-analysis of the original 5-year Lung Health Study data (Table 1) [26]. Total mortality consisted of mortality related to severe exacerbations, other COPD-attributable mortality, and mortality due to other causes (Table 2). The model was implemented in Mathematica 7 and was validated by performing several internal checks and by comparing the results with other models [29].

Tiotropium COPD model (represented by Rutten-van Mölken) [18]

The 5-year version of the tiotropium COPD model was implemented in Excel and published in 2007. The model was developed to estimate the cost-effectiveness of tiotropium (Boehringer Ingelheim) versus other bronchodilators. The state-transition cohort model with a cycle length of 1 month has four health states: moderate, severe, and very severe COPD and death. Exacerbations were modeled as events within severity states and specified as nonsevere or severe. The COPD population at the start reflected the patient population included in the tiotropium trials. These were mainly patients with severe and very severe COPD. The distribution of the lung function of patients with moderate COPD in this population was located at the severe end of the lung function range for moderate COPD. Disease progression in the first year was based on data from six tiotropium trials. Because these trials showed an increase in lung function in the first year in part of the patients, backward transition to a less severe COPD stage is possible in the first year. For the following years, annual decline in lung function was obtained from the Lung Health Study (Table 1). Mortality was modeled as all-cause mortality specified by COPD severity. Exacerbation-related mortality was not modeled separately (Table 2). One-year model results were validated against 1-year trial data, resulting in comparable numbers of exacerbations [30].

Roflumilast COPD model (represented by Samyshkin) [19,31,32]

The recently published Roflumilast COPD model (2012–2013) was developed to estimate the cost-effectiveness of roflumilast versus several comparators. The model, whose development was financed by Takeda, was a state-transition cohort-based model implemented in TreeAge Pro Suite 2009 with a Microsoft Excel front-end. The structure of the original model included three health states: severe COPD, very severe COPD, and death; the cycle length in the model was 1 month. For the purpose of this exercise, the model was extended with the state "moderate COPD." Exacerbations are modeled as events that can occur within each of the COPD severity states, and are specified as moderate or severe. The population in the severe and very severe states of the model was based on the patient population of the long-acting beta agonist-alone group of two large roflumilast trials. Disease progression, that is, annual decline in lung function, was derived from the Lung Health Study (Table 1). Mortality was modeled as a combination of background mortality estimated from the general population from life tables adjusted to the standardized mortality ratio for COPD and mortality due to severe exacerbations (Table 2).

German comprehensive care COPD model (by Menn, represented by Wacker) [20]

The German comprehensive care COPD model published in 2012 was developed with financial support of the Competence Network Asthma/COPD (Federal Ministry of Education and Research). The model was implemented in TreeAge Pro 2007. The main purpose of the cohort model was to evaluate the cost-effectiveness of COPD interventions in the German context. The model has seven states: four COPD severity states, one state after lung volume reduction surgery, one state after lung transplantation, and death. Cycle length is 3 months. Mild, moderate, and severe exacerbations are modeled as events within disease states. Starting point of the simulation is a 45-year-old patient with mild COPD. Disease progression for mild and moderate COPD was based on the Lung Health Study specified by smoking status. The Inhaled Steroids in Obstructive Lung Disease and Towards a Revolution in COPD Health trials were used to obtain estimates of the annual decline in severe COPD in smokers (Table 1). All-cause mortality was divided into mortality in stable disease, mortality associated with severe exacerbations, and very severe COPD mortality associated with surgery and transplantation (Table 2). Model validation was performed by comparing the results with observed data: the severity distribution among smokers and quitters in the Lung Health Study and the total exacerbation probabilities of the TRISTAN trial.

Table 3 – Input variables to standardize the reference scenario.

Variable	Value*
Sex	Male
Age (y)	65
Smoking status	Ex-smoker
COPD disease severity†	Moderate COPD (GOLD guidelines) or a mean FEV_1 of 65% predicted
Baseline total exacerbation frequency by COPD severity†	0.82 (0.26), 1.17 (0.15), 1.61 (0.06), 2.10 (0.36)
Baseline severe exacerbation frequency by COPD severity†	0.11 (0.14), 0.16 (0.07), 0.22 (0.01), 0.28 (0.13)
Mortality due to causes other than COPD	1.5% (0.23)
Utilities during stable disease by COPD severity†	0.90 (0.11), 0.787 (0.008), 0.750 (0.0093), 0.647 (0.0241)
Annual costs for treating stable disease by COPD severity†	€100 (15), €300 (45), €650 (98), €1200 (180)
Reduction in baseline utility due to a moderate exacerbation	1-mo cycle: 18% (2.7), 3-mo cycle: 6% (0.9), 1-y cycle: 1.5% (0.22)
Reduction in baseline utility due to severe exacerbation	1-mo cycle: 60% (9), 3-mo cycle: 20% (3), 1-y cycle: 5% (0.75)
Costs for a moderate and severe exacerbation, respectively	€100 (15), €4000 (600)

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 s; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SE, standard error.

* Data are mean (SE).

† Four COPD severity stages based on the GOLD guidelines: mild ($FEV_1 \geq 80\%$ of predicted), moderate ($50\% \leq FEV_1 < 80\%$), severe ($30\% \leq FEV_1 < 50\%$), and very severe COPD ($FEV_1 < 30\%$).

Standardization of the Reference Scenario

To increase comparability among the different models, groups were requested to run their model for a male patient or cohort of male patients with moderate COPD, ex-smoking, and aged 65 years. Furthermore, groups were asked to standardize exacerbation frequencies, mortality due to other causes, utilities, and costs (Table 3). The probability distribution for the parameters used in the probabilistic sensitivity analysis was not standardized. All analyses were performed using a 3% discount rate for both effects and costs. The probabilities for end-stage treatment options and mild exacerbations were set to zero if included in the model. A model simulation with the standardized parameters was considered the reference scenario.

Hypothetical Interventions

Four different interventions reflecting the broad range of possible interventions available for COPD were defined. Effect sizes and costs were hypothetical and not based on any clinical trial. The first intervention assumed a 20% reduction in annual decline in lung function or, if this was not possible, a 20% reduction in transition probabilities between COPD severity stages. Annual costs for this intervention were assumed to be €200 per patient. The second intervention assumed a 25% reduction in the total exacerbation frequency, with annual costs of €400 per patient. When applying this intervention, groups were asked to keep the ratio between exacerbations with a different severity constant. For intervention three, groups modeled a 10% reduction in total mortality. Annual costs were €300 per patient. The fourth intervention consisted of the combination of all three effects of the first three interventions, 20% reduction in annual decline in lung function, 25% reduction in exacerbation frequency, and 10% reduction in mortality, with annual costs of €700 per patient.

Outcomes

Each modeling group ran the hypothetical interventions for two different time horizons: 5 year and lifetime. For both time horizons, groups reported the following outcomes: mean number of exacerbations per patient, mean number of life-years, quality-adjusted life-years (QALYs) gained and incremental costs per patient, and the incremental cost-effectiveness ratio (ICER) compared with the reference scenario. In addition, the severity distribution over the COPD severity stages after 5 years and the percentage of patients who died were provided for the 5-year horizon, while for the lifetime analysis the time spent in each severity stage was reported.

Uncertainty

For the second part of the exercise, groups provided details about uncertainty around the outcomes of intervention four, a 20% (SE 4) reduction in annual decline in lung function, 25% (SE 5) reduction in exacerbation frequency, and 10% (SE 2) reduction in mortality, with annual costs of €700 per patient using a 5-year time horizon. Ninety-five percent confidence intervals were given around the mean number of QALYs and mean costs for the intervention and the usual-care scenario as well as the difference in QALYs and costs. Furthermore, each modeling group displayed the uncertainty around the outcomes in an acceptability curve with willingness-to-pay values between €0 and €100,000 per QALY.

Results and Explanations

Comparison of Reference Scenario

Five-year model outcomes for the reference scenario after standardization of requested input parameters are shown in Figure 1. In five out of seven models, the percentage of patients still in moderate COPD after 5 years was around 60% to 70%. In the

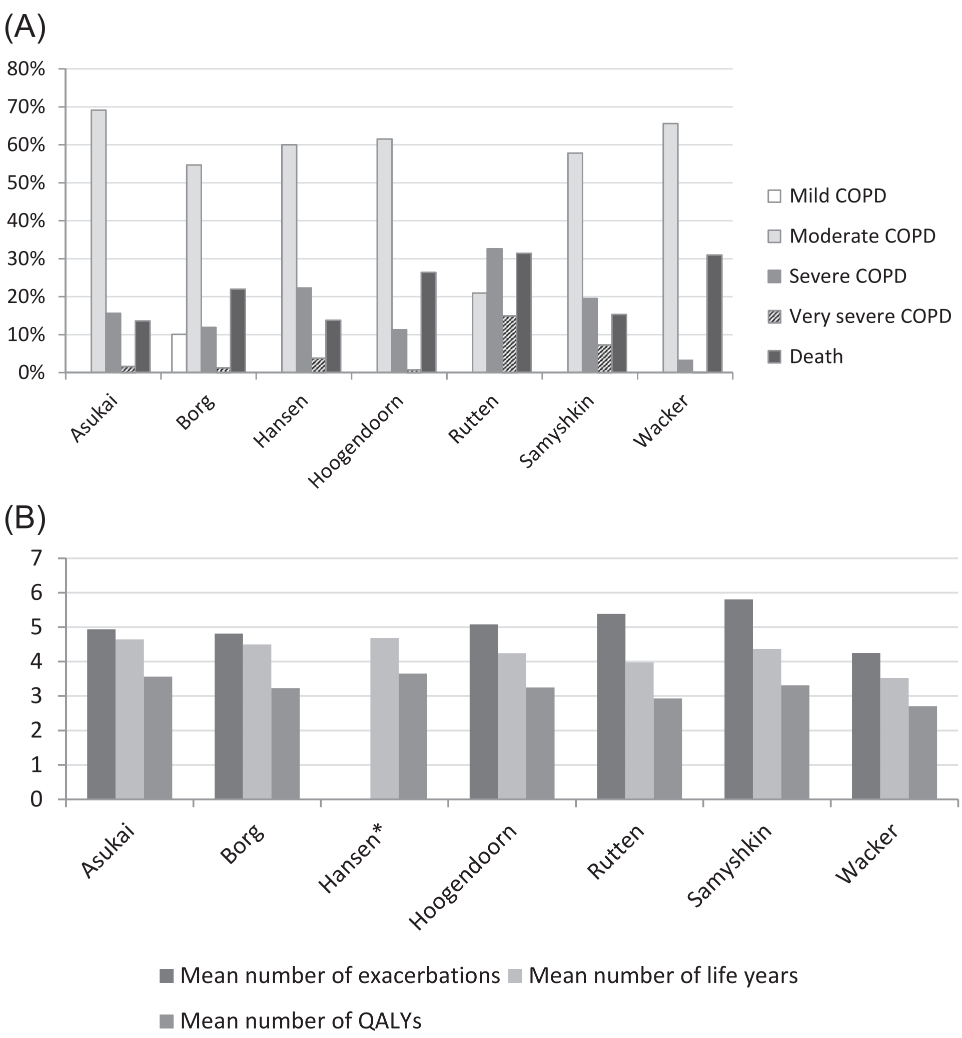

Fig. 1 – Comparison of 5-year model outcomes for the reference scenario, discount rate both costs and effects 3%. (A) Severity distribution and mortality and (B) mean number of exacerbations and (quality-adjusted) life-years per patient. COPD, chronic obstructive pulmonary disease; QALYs, quality-adjusted life-years. *Total exacerbations was not an outcome in the model of Hansen.

model of Borg et al., 10% of the patients regressed to mild COPD and about 55% remained in moderate COPD, while in the model of Rutten, 20% of the patients remained in moderate COPD and 32% progressed to severe COPD. Further comparison of the seven models showed that the percentage of patients who died after 5 years ranged from 14% to 31%. The mean number of QALYs varied between 2.7 and 3.7. The mean 5-year costs per patient for the models of Asukai, Borg, and Menn/Wacker were around €4000 (range €3743–€4001). For the other four models, the mean costs varied between €5097 for the model of Samyshkin and €5806 for the model of Hansen. Differences were larger but comparable in ranking for a lifetime time horizon (data not shown). Despite the standardization, the outcomes for the reference scenario still showed substantial variation between the models, especially regarding survival.

Intervention One: Disease Progression

For the models of Asukai, Hoogendoorn, and Samyshkin, this intervention was implemented as a 20% reduction in annual decline in lung function. The other models applied a 20% reduction in transition probabilities to worse states. Based on the results, the effect of altering decline or altering probabilities seemed minimal. Using a 5-year time horizon, the differences in cost-effectiveness ratios for intervention one (Table 4) could mainly be explained by the differences in transition probabilities between the models, except for the models of Borg and Hansen. In general, models with high transition probabilities to worse severity stages, such as the model of Rutten (see Table 1), benefit most from a 20% reduction in transition probabilities and thus reported the lowest ICERs. In accordance with this, models with low transition probabilities, such as the models of Menn/Wacker and Hoogendoorn, found a high ICER. The model of Hansen et al. found a high ICER in comparison with other models given the relatively high transition probabilities (Table 1). The model of Borg reported a very high cost-effectiveness ratio because of a (nearly) zero difference in QALYs, which could be explained by poor precision due to a small number of simulated patients, or that some patients spend time in mild COPD in which there is relatively little disease progression risk to be reduced (thus little benefit of the intervention) while the cost of the intervention is still accrued.

Using a lifetime horizon, the ICER is affected by a combination of the transition probabilities to the next severity stage as well as the probability of death. The model of Menn/Wacker with a low transition probability to more severe stages and a high probability to die found the highest ICER (Table 5) because the absolute gain in effect is relatively low and the time to gain effect is relatively short, on average 7.2 life-years. The model of Asukai with the lowest annual mortality probability reported the most favorable ICER because the time to gain effect was the longest, on average 14.8 life-years.

Intervention Two: Exacerbations

Differences in outcomes for intervention two, a 25% reduction in exacerbation frequency, could mainly be explained by differences in exacerbation-related mortality. For the 5-year time horizon, the model of Menn/Wacker and Hoogendoorn both resulted in low costs per QALY (Table 4) because of the relatively high mortality associated with exacerbations in comparison with other models (see Table 2). The models of Asukai and Rutten reported a high ratio because exacerbations did not have an impact on mortality, so the gain in the QALYs was the result of a gain only in quality of life and not in life-years. The model of Rutten et al. reported a lower ICER than did the model of Asukai et al. because in the first model patients progress faster to a more severe health state associated with higher exacerbation rates and therefore higher absolute gains in QALYs compared with the situation in which patients remain in moderate COPD for a longer time period. The model of Hansen reported the highest ICER,

Table 4 – Five-year cost-effectiveness results for the four hypothetical interventions compared with no intervention.

Intervention	Asukai	Borg	Hansen	Hoogendoorn	Rutten	Samyshkin	Wacker
Intervention one: 20% reduction in disease progression							
Difference in QALYs	0.012	0.00020	0.0077	0.0035	0.039	0.018	0.0020
Difference in costs (€)	842	880	912	816	561	734	695
Cost-effectiveness ratio (€)	69,000	4,400,500	118,300	234,500	14,400	40,200	347,500
Intervention two: 25% reduction in exacerbations							
Difference in QALYs	0.018	0.024	0.0089	0.056	0.020	0.046	0.075
Difference in costs (€)	1,249	1,350	942	961	739	926	844
Cost-effectiveness ratio (€)	68,900	56,000	106,300	17,300	37,000	20,200	11,300
Intervention three: 10% reduction in mortality							
Difference in QALYs	0.026	0.017	0.045	0.034	0.048	0.025	0.047
Difference in costs (€)	1,431	1,465	1,618	1,345	1,315	1,361	1,140
Cost-effectiveness ratio (€)	55,500	87,200	35,700	39,300	27,400	55,400	24,300
Intervention four: combination of effects intervention one to three							
Difference in QALYs	0.056	0.10	0.054	0.091	0.11	0.086	0.12
Difference in costs (€)	2,608	2,903	2,570	2,295	1,854	2,173	2,002
Cost-effectiveness ratio (€)	46,700	27,800	47,400	25,300	17,400	25,300	16,800

QALYs, quality-adjusted life-years.

Table 5 – Lifetime cost-effectiveness results for the four hypothetical interventions compared with no intervention.

Intervention	Asukai	Borg	Hansen	Hoogendoorn	Samyshkin	Wacker
Intervention one: 20% reduction in disease progression						
Difference in QALYs	0.357	0.110	0.083	0.081	0.270	0.030
Difference in costs (€)	1,893	4,051	1,735	1,633	1,591	1,427
Cost-effectiveness ratio (€)	5,300	36,700	21,000	20,100	5,900	47,600
Intervention two: 25% reduction in exacerbations						
Difference in QALYs	0.060	0.317	0.087	0.366	0.205	0.382
Difference in costs (€)	2,953	7,917	1,629	2,419	2,113	2,143
Cost-effectiveness ratio (€)	49,500	25,000	18,600	6,600	10,300	5,600
Intervention three: 10% reduction in mortality						
Difference in QALYs	0.581	0.255	0.616	0.347	0.259	0.336
Difference in costs (€)	4,211	7,012	5,175	3,463	3,568	2,762
Cost-effectiveness ratio (€)	7,300	27,500	8,400	10,000	13,800	8,200
Intervention four: combination of effects intervention one to three						
Difference in QALYs	1.030	0.533	0.714	0.806	0.751	0.755
Difference in costs (€)	6,938	14,579	6,886	6,018	5,595	5,146
Cost-effectiveness ratio (€)	6,700	27,300	10,000	7,500	7,400	6,800

QALYs, quality-adjusted life-years.

which was unexpected given that this model included an increased mortality risk associated with both moderate and severe exacerbations. When models were ranked according to the ICERs for the lifetime time horizon, the ranking was comparable to the 5-year time horizon (Table 5).

Intervention Three: All-Cause Mortality

Results of intervention three, a 10% reduction in total mortality, could be explained by the input values for mortality used in the models (Table 2). The 5-year results showed that in the models of Menn/Wacker and Rutten for which mortality probabilities in the first year were the highest, around 7%, a 10% reduction in mortality probability had the highest impact and therefore the ICERs were the lowest (Table 4). For the models of Asukai and Samyshkin with the lowest mortality probabilities, around 3%, the ICERs were the highest. Based on the ranking of the mortality probabilities in the first year, the ICER for the Borg model was higher than expected when compared with the other models, while the ICER for the model of Hansen was lower than expected. Results of the ICERs for the lifetime time horizon were comparable in ranking to the 5-year results (Table 5), except for the model of Asukai, which resulted in the lowest ICER although this model had the lowest mortality probability in the first year.

Intervention Four: Combination of Three Effects

In all models, the three effects of intervention four were not calibrated. This means that it was not taken into account that, for example, a reduction in exacerbation frequency already leads to a reduction in mortality in most models. For the current exercise, effects of intervention four were implemented independently. As a result, the gain in QALYs for intervention four was fairly comparable to the sum of QALYs gained in the first three interventions in six out of seven models. Differences in cost-effectiveness results between the models for intervention four are more difficult to explain because these are the result of simultaneous changes in three different parameters. Mortality, however, seems to be the driving factor. The model of Menn/Wacker using the highest values for total mortality and exacerbation-related mortality but the slowest disease progression reported the most favorable ICER. The model of Asukai, which used moderate values for disease progression, the lowest value for total mortality, and no additional mortality for exacerbations, found one of the highest ICERs (Table 4).

Uncertainty

A list of parameters for which uncertainty is included in the models can be found in Appendix I in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2014.03.1721. Figure 2 shows the 95% confidence intervals around the difference in QALYs and costs for intervention four using a 5-year time horizon. Figure 3 shows the acceptability curve for intervention four. Six models showed curves that had roughly the same shape, with a relatively steep increase in the probability of the intervention being cost-effective. The thresholds at which a 90% cost-effectiveness probability was reached varied from €30,000 to €60,000 for these models. The acceptability curve for the model of Hansen increased very gradually and reached a 90% confidence level at a €85,000 threshold.

Discussion

This cross-model validation study aimed to compare different COPD models by explaining the results of the evaluation of four hypothetical interventions that affected lung function decline, COPD exacerbations, all-cause mortality, or all three of these on the basis of differences in model structure and input parameters. Differences in the results of the deterministic analyses could, in general, be explained by structural uncertainty and by the rank order of input values used for disease progression, exacerbation-related mortality, and total mortality in the models. Mortality was the most important factor determining the QALY outcomes, especially for a lifetime time horizon. For example, for the intervention that assumed a 20% reduction in disease progression, the differences in transition probabilities to more severe disease states were of less importance for the lifetime results than the values used as input for total mortality. A substantial part of the differences in the results of the deterministic analyses was the result of structural uncertainty in each model. Structural uncertainty is characterized by assumptions about the structure

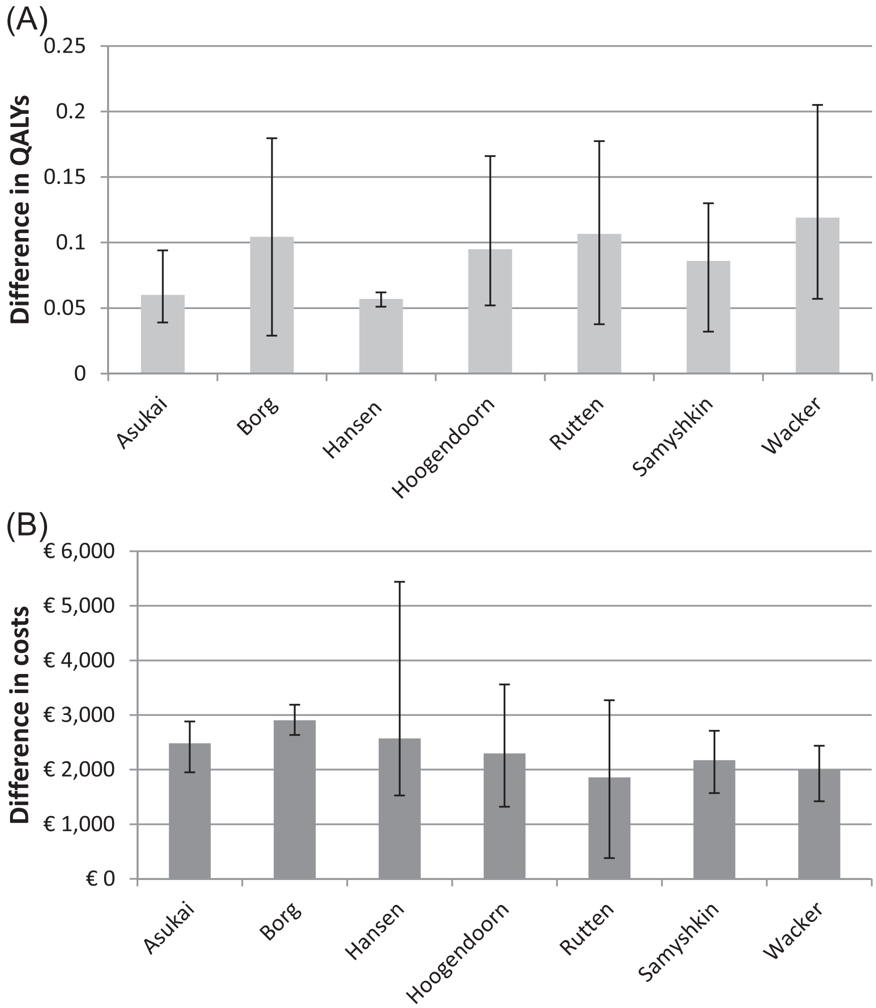

Fig. 2 – Uncertainty around the results of intervention four for a 5-year time horizon: mean and 95% confidence intervals around (A) difference in QALYs and (B) difference in costs. QALYs, quality-adjusted life-years.

of the model, such as the number of COPD severity states, the possibility of backward transition to less severe states, and the inclusion of exacerbation-related mortality [33]. Mortality was one of the parameters with the most variation in the way it was modeled. Most models specified mortality into two types: non–COPD-related mortality and COPD-related mortality. The concept of non–COPD-related mortality, however, does not mean the same in all models. Some models define this as the all-cause

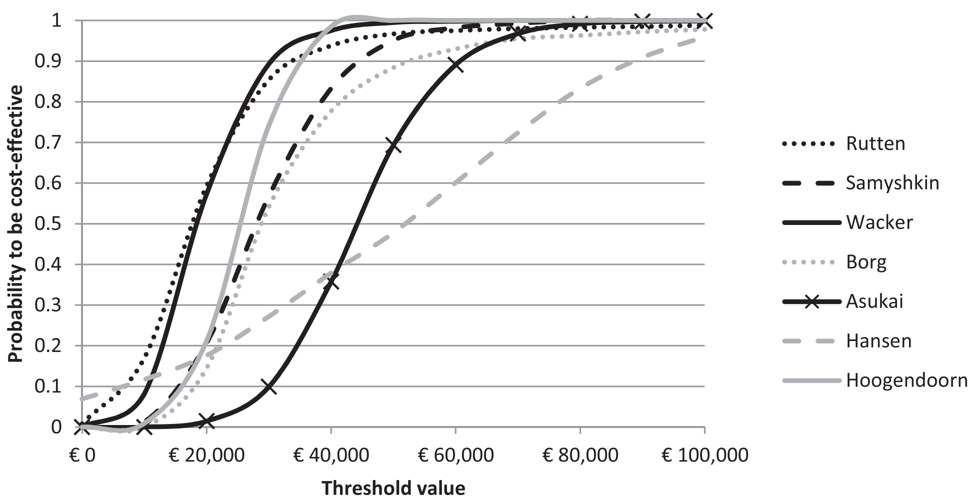

Fig. 3 – Acceptability curve for intervention four compared with no intervention, 5-year time horizon.

mortality rate in the general population, whereas other models define this as all non–COPD-related mortality among patients with COPD, including the increased risk to die of other—mostly smoking-related—diseases (Table 2). In some models, COPD-related mortality equals exacerbation-related mortality, whereas in other models exacerbation-related mortality is part of COPD-related mortality and also includes COPD-attributable mortality that is not related to exacerbations (Table 2). These differences in definition hinder comparison between models with respect to mortality. These differences also cause the same intervention (e.g., an intervention that reduces the exacerbation rate with 25%) to have different mortality effect sizes, depending on the model. Therefore, it is of utmost importance to aim for consensus on how mortality is best modeled and what data to use for this. Modeling mortality from COPD exacerbations separately obviously leads to more favorable cost-effectiveness ratios of interventions that reduce the exacerbation rate than not doing so.

When comparing the results of the probabilistic sensitivity analysis for intervention four, differences result not only from differences in model structure and input values but also from parameter uncertainty. Parameter uncertainty results from the fact that a parameter value is estimated from a sample and the "true" value is unknown. This uncertainty is represented by a probability distribution for each parameter [33]. Although the uncertainty around utilities, costs, COPD exacerbation probabilities, and mortality from causes other than COPD was standardized by providing a standard error (SE), the differences in uncertainty around the estimated difference in QALYs and costs for intervention four were still substantial. This was probably caused by the uncertainty around other nonstandardized parameters, such as disease progression and COPD-related mortality, and/or differences in the type of probability distributions around parameters used in the probabilistic sensitivity analysis. For example, there is a more than 2-fold difference between the models in the point estimate of the QALY gain due to intervention four (from 0.054 to 0.12) and a 14-fold difference in the width of the 95% confidence interval around the QALY gain (from 0.011 to 0.151) (Fig. 2). The probability that intervention four was cost-effective at a threshold value of €50,000 ranged from 45% to almost 100%.

Differences with regard to structure and input parameters can often be explained by the model's purpose. Some of the models are more universal in the sense that they can be used for a range of problems, while other models were built for a specific application, for example, the extrapolation of the results of a trial. The results of the indacaterol model, for example, were mainly affected by mortality being independent from exacerbations. The primary end point in the indacaterol trials used as input for the model was the change in lung function in the first 12 weeks. Therefore, less emphasis was put on modeling the effect of exacerbations on mortality. The results for the tiotropium model could mainly be explained by the high disease progression in this model. In this model, disease progression for the first year was based on data from six trials. These trials mainly included patients with severe and very severe COPD. The few patients with moderate COPD (about 20% of all patients in the original trials) had a forced expiratory volume in 1 second % predicted close to the cutoff point for severe COPD, resulting in a high probability to move from moderate to severe COPD. In the original, nonstandardized version of the model, this fast progression is compensated by a relatively high probability to move back from severe to moderate COPD in the first year because of an improvement in lung function in part of the patients after start of the medication. Because the scenarios described a moderate patient instead of a patient population with mixed severity, however, the percentage of patients moving back from severe to moderate is very small. Moreover, the definition of the health states in this model was based on prebronchodilator forced expiratory volume in 1 second, which increases the severity of the populations and the probability to move into a more severe health state. In retrospect, this model seems less suitable to use for analyses for a cohort of patients with moderate COPD.

Cross-validation of models may increase confidence in the results if similar results are found by different models [13]. One of the limitations of this approach, however, is that finding similar results does not mean that results are valid. Agreement may be the result of using the same structural assumptions and data sources for input. The Lung Health Study, for example, was used as a single or combined data source by five of the seven models to estimate disease progression. Another limitation of our current cross-validation exercises is that by running hypothetical interventions with the models only the differences between the models can be explained, but not which models perform best. Although the effectiveness of the interventions lies within the range of effect sizes observed in COPD interventions, using hypothetical interventions may also have reduced the clinical relevance. Real-life data are needed to further validate the models. During the Mount Hood Challenge Meetings for diabetes modeling, this was done by performing simulations of outcomes for patients published in clinical trials [34–36]. Validation against real-life data may be a topic of future COPD modeling meetings. The availability of well-performed COPD trials with a follow-up of several years is however limited [37,38].

To make the results of the treatment scenarios more comparable, part of the input parameters was standardized. Models were asked to run the scenarios for a male, ex-smoking patient aged 65 years with moderate COPD. All models were able to standardize for disease severity, exacerbation frequency, utilities, and costs. For the model of Hansen, standardization of exacerbation-related parameters, however, was done differently than in the other models, because the total number of exacerbations was not an outcome in this model, only exacerbation days. Therefore, the standardized input values for exacerbation utility decrement and costs were divided by the mean number of days of an exacerbation and applied as the mean utility decrement or costs per exacerbation day. Standardization with respect to other parameters was occasionally difficult. The model of Rutten was not standardized for sex and age and the model of Borg was not standardized for sex, because these patient characteristics were not included as model parameters. Not standardizing for age could have had a large effect, especially on the results of the lifetime analysis. The maximum time horizon for the model of Rutten, however, was 5 years. Only three models [16,17,20] were able to standardize for smoking status, because smoking status was not considered in the other models. The model of Hoogendoorn was the only model taking into account restart rates for smoking. The effect of these restart rates on the results for the current analyses was minimal; after 5 years, more than 95% of the cohort was still ex-smoker. Finally, the model of Borg was not able to standardize background mortality, while in the model of Rutten only all-cause mortality could be standardized, because this is the only type of mortality included in this model. The type of mortality that is standardized, however, seemed of minor importance because total mortality rates are different between models anyway. The choice of parameters needing standardization was made by the steering committee and comprised finding a balance between getting comparable results versus maintaining the specific character of the models.

The severity distribution for COPD used in all models was based on the degree of airflow limitation. In 2011, the Global Initiative for Chronic Obstructive Lung Disease committee proposed a new grading of COPD severity based on airflow obstruction, exacerbations, and symptoms to better capture the complexity of COPD. Currently, the prognostic value of this new classification is being investigated [39–41]. Changes in the structure of the models to this new classification need to be considered if treatment effects and cost-effectiveness results are found to be different between the different severity classes. This would also, however, have an effect on the type of model. All models included in the current article were Markov models. Using more parameters than lung function alone to define COPD severity would increase the number of health states exponentially and substantially increase the complexity of the model structure as well the input data required. Current COPD models under development or recently published models are therefore exploring microsimulation modeling or structured equation modeling [42,43]. The advantage of such approaches is that heterogeneity of the patient population can be better taken into account in the model, which is becoming more and more important because treatment for COPD is increasingly personalized.

In conclusion, this article describes the comparison of seven cost-effectiveness models for COPD by means of the results of four hypothetical interventions and tries to explain the differences in outcomes on the basis of differences in structure and input data for mortality and disease progression. Mortality was shown to be the most important factor determining the differences in cost-effectiveness outcomes. Validation against real-life data is needed to further validate the models.

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Supplemental Materials

Supplemental material accompanying this article can be found in the online version as a hyperlink at http://dx.doi.org/10.1016/j.jval.2014.03.1721 or, if a hard copy of article, at www.valueinhealthjournal.com/issues (select volume, issue, and article).

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